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(54) Title: POLYHYDROXYALKANOATE NERVE REGENERATION DEVICES

(57) Abrégé/Abstract:

Nerve regeneration devices are provided with improved rates of axonal regeneration, and methods for their manufacture are also disclosed. The devices are formed from a biocompatible, absorbable polymer, known as poly- 4hydroxybutyrate. Growth factors, drugs, or cells that improve nerve regeneration may be incorporated into the devices. The devices are administered by implantation preferably without the use of sutures. In one aspect, the device is in the form of a wrap that can be used easily to capture the severed nerve bundle ends during surgery, and formed into a conduit in situ. If desired, the edges of the wrap can be melted together to seal the conduit, and hold it in place. A major advantage of the device is that it does not need to be removed after use since it is slowly degraded and cleared by the patient's body, yet remains functional in situ beyond the time required for nerve regeneration, and helps exclude scar tissue. The device also degrades in a cell-friendly manner, and does not release highly acidic or inflammatory metabolites. Furthermore, the device is flexible, strong, does not crush the regenerating nerve, is easy to handle, reduces surgical time by eliminating the need to harvest an autologous graft, and allows the surgeon to repair the nerve without a prolonged delay.

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(54) Title: POLYHYDROXYALKANOATE NERVE REGENERATION DEVICES

(57) **Abstract:** Nerve regeneration devices are provided with improved rates of axonal regeneration, and methods for their manufacture are also disclosed. The devices are formed from a biocompatible, absorbable polymer, known as poly-4hydroxybutyrate. Growth factors, drugs, or cells that improve nerve regeneration may be incorporated into the devices. The devices are administered by implantation preferably without the use of sutures. In one aspect, the device is in the form of a wrap that can be used easily to capture the severed nerve bundle ends during surgery, and formed into a conduit in situ. If desired, the edges of the wrap can be melted together to seal the conduit, and hold it in place. A major advantage of the device is that it does not need to be removed after use since it is slowly degraded and cleared by the patient's body, yet remains functional in situ beyond the time required for nerve regeneration, and helps exclude scar tissue. The device also degrades in a cell-friendly manner, and does not release highly acidic or inflammatory metabolites. Furthermore, the device is flexible, strong, does not crush the regenerating nerve, is easy to handle, reduces surgical time by eliminating the need to harvest an autologous graft, and allows the surgeon to repair the nerve without a prolonged delay.

POLYHYDROXYALKANOATE NERVE REGENERATION DEVICES

Background of the Invention

5 The present invention generally relates to nerve regeneration devices derived from poly-4-hydroxybutyrate and its copolymers.

10 Several reports have described the use of alternative methods to repair severed nerves to restore both motor and sensory function that are lost when a nerve is injured. Existing microsurgical techniques attempt to align the severed nerve endings in a tension-free manner by suturing. If the defect is 15 large, a nerve graft is utilized. This approach can however cause additional trauma to the nerve endings resulting in the formation of scar tissue that prevents the regenerating axons in the proximal stump (the nerve ending still connected to the spinal cord or dorsal root) from reconnecting to the distal stump (the nerve ending no 20 longer connected to the spinal cord). Donor site morbidity can also result if a nerve graft is used.

To improve upon this approach, researchers have investigated alternative sutureless methods for reconnecting severed nerve endings, and also to try and avoid the use of grafts 25 to bridge larger nerve gaps. Adhesives such as cyanoacrylate glue and fibrin have been evaluated as well as welding tissue with carbon dioxide lasers, but these methods apparently did not improve results (Hazari et al. J. Hand Surgery, 24B: 291-295, 1999). The use of tubular conduits has also been tested as a 30 method to provide a channel that can prevent or retard the infiltration of scar-forming tissue, potentially increase the concentration of nerve growth factor locally within the conduit,

and also to bridge larger defects without the use of a graft. In this approach the severed nerve endings are drawn into proximity in a manner that minimizes additional trauma by placing them inside opposite ends of the nerve guide channel.

5 Various materials have been tested as candidates for nerve channel conduits, and some have been used clinically. These include silicone rubber, polyglactin mesh, acrylic copolymer tubes, and other polyesters. It has been reported by PCT WO 88/06866 by Aebischer et al., however, that there are significant shortcomings
10 with devices prepared from these materials. These include inflammatory responses, formation of scar tissue, and loss of sensory or motor function. Two companies, Integra Lifesciences and Neuroregen, LLC, have commercialized nerve channel conduits made from collagen (NeuraGen Nerve GuideTM) and
15 polyglycolic acid (NeurotubeTM) to bridge small nerve gaps.

To improve upon these results, several researchers have investigated the use of poly-3-hydroxybutyrate (PHB) as a material for nerve regeneration, and the use of growth factors and Schwann cells to prevent nerve cell death and promote regeneration. PCT
20 WO 88/06866 to Aebischer et al. discloses tubular piezoelectric nerve conduits including a device formed from PHB. Hazari et al. in Vol. 24B J. Hand Surgery, pp. 291-295 (1999), Ljungberg et al. in Vol. 19 Microsurgery, pp. 259-264 (1999), and Hazari et al. in Vol. 52 British J. Hand Surgery, pp. 653-657 (1999) also disclose
25 PHB conduits for nerve regeneration. PCT WO 03/041758 to Wiberg discloses a nerve repair unit comprising PHB and an alginate matrix containing human Schwann cells, and PCT WO 01/54593 also discloses PHB conduits that include Schwann cells. Hazari et al. in Vol. 52 British J. Hand Surgery, pp. 653-657
30 (1999), for example, discloses a rate of axonal regeneration using a PHB conduit to bridge a 10 mm nerve gap in a rat sciatic nerve of

approx. 10% at 7 days, 50% at 14 days, and complete regeneration at 30 days.

Despite these positive results, it would still be highly desirable to increase the rate of axonal regeneration so that the 5 rate is at least comparable to that obtained using a nerve graft. It would also be desirable to improve the degree of restoration of motor and/or sensory function.

Accordingly, it is an object of this invention to provide an improved nerve guide conduit for nerve regeneration that allows a 10 rapid axonal regeneration.

It is a further object of this invention to provide a nerve guide conduit that can be combined with cells or growth factors that promote nerve regeneration and/or prevent or slow nerve cell death.

15 It is yet another object of this invention to provide methods for preparing and implanting the nerve regeneration devices.

Summary of the Invention

Nerve regeneration devices are provided with improved rates of axonal regeneration, and methods for their manufacture 20 are also disclosed. The devices are formed from a biocompatible, absorbable polymer, known as poly-4-hydroxybutyrate. Growth factors, drugs, or cells that improve nerve regeneration may be incorporated into the devices. The devices are administered by implantation preferably without the use of sutures. In one aspect, 25 the device is in the form of a wrap that can be used easily to capture the severed nerve bundle ends during surgery, and formed into a conduit in situ. If desired, the edges of the wrap can be melted together to seal the conduit, and hold it in place. A major advantage of the device is that it does not need to be removed after 30 use since it is slowly degraded and cleared by the patient's body, yet remains functional in situ beyond the time required for nerve

regeneration, and helps exclude scar tissue. The device also degrades in a cell-friendly manner, and does not release highly acidic or inflammatory metabolites. Furthermore, the device is flexible, strong, does not crush the regenerating nerve, is easy to 5 handle, reduces surgical time by eliminating the need to harvest an autologous graft, and allows the surgeon to repair the nerve without a prolonged delay.

Detailed Description of the Invention

Devices for the repair of severed or damaged nerves are 10 provided. These devices can be used instead of suture-based repairs, grafts to repair nerves, and/or where it is desirable to administer locally nerve cells, growth factors or other substances that promote nerve regeneration.

I. Definitions

15 Poly-4-hydroxybutyrate means a homopolymer comprising 4-hydroxybutyrate units. It may be referred to as PHA4400 or P4HB. Copolymers of poly-4-hydroxybutyrate mean any polymer comprising 4-hydroxybutyrate with one or more different hydroxy acid units.

20 Biocompatible refers to materials that are not toxic, and do not elicit prolonged inflammatory or chronic responses *in vivo*. Any metabolites of these materials should also be biocompatible.

25 Biodegradation means that the polymer must break down *in vivo*, preferably in less than two years, and more preferably in less than one year. Biodegradation refers to a process in an animal or human. The polymer may break down by surface erosion, bulk erosion, hydrolysis, or a combination of these mechanisms.

II. Polymers

30 The polymers should be biocompatible and biodegradable. The polymers are typically prepared by fermentation. Preferred polymers are poly-4-hydroxybutyrate and copolymers thereof.

Examples of these polymers are produced by Tepha, Inc. of Cambridge, MA using transgenic fermentation methods, and have weight average molecular weights in the region of 50,000 to 1,000,000.

- 5 Poly-4-hydroxybutyrate (PHA4400) is a strong pliable thermoplastic that is produced by a fermentation process (see U.S. Patent No. 6,548,569 to Williams et al.). Despite its biosynthetic route, the structure of the polyester is relatively simple. The polymer belongs to a larger class of materials called
- 10 polyhydroxyalkanoates (PHAs) that are produced by numerous microorganisms (for reviews see: Steinbüchel, A. (1991) Polyhydroxyalkanoic acids, in Biomaterials, (Byrom, D., Ed.), pp. 123-213. New York: Stockton Press. Steinbüchel, A. and Valentin, H.E. (1995) FEMS Microbial. Lett. 128:219-228; and Doi, 1990 in
- 15 Microbial Polyesters, New York: VCH). In nature these polyesters are produced as storage granules inside cells, and serve to regulate energy metabolism. They are also of commercial interest because of their thermoplastic properties, and relative ease of production. Several biosynthetic routes are currently known to produce
- 20 PHA4400. Chemical synthesis of PHA4400 has been attempted, but it has been impossible to produce the polymer with a sufficiently high molecular weight necessary for most applications, see Hori et al. 1995, Polymer 36:4703-4705.

- 25 Tepha, Inc. (Cambridge, MA) produces PHA4400 and has filed a Device Master File with the United States Food and Drug Administration (FDA) for PHA4400. Methods to control molecular weight of PHA polymers have been disclosed by U.S. Patent No. 5,811,272 to Snell et al., and methods to purify PHA polymers for medical use have been disclosed by U.S Patent No. 6,245,537 to
- 30 Williams et al. PHAs with degradation rates *in vivo* of less than

one year have been disclosed by U.S. Patent No. 6,548,569 to Williams et al. and PCT WO 99/32536 to Martin et al. PHAs are known to be useful to produce a range of medical devices. For example, U.S. Patent No. 6,514,515 to Williams 5 discloses tissue engineering scaffolds, U.S. Pat. Nos. 6,555,123 and 6,585,994 to Williams and Martin discloses soft tissue repair, augmentation and viscosupplementation, U.S. Patent No. 6,592,892 to Williams discloses flushable disposable polymeric products, and PCT WO 01/19361 to Williams and Martin discloses 10 PHA prodrug therapeutic compositions. Other applications of PHAs have been reviewed by Williams and Martin, 2002, in *Biopolymers: Polyesters, III* (Doi, Y. and Steinbüchel, A., Eds.) vol. 4, pp. 91-127. Weinheim: Wiley-VCH.

III. Method of Manufacture and Administration

15 The nerve regeneration devices are preferably manufactured in a porous form by methods such as particulate leaching, phase separation, lyophilization, compression molding, or melt extrusion into fibers and subsequent processing into a textile construct. For example the device could be fabricated as a 20 nonwoven, woven or knitted structure. Preferably, the pores of the device are between 5 and 500 μm in diameter. The device should be slightly longer than the nerve gap to be repaired. Preferably the device is about 2 mm longer at either end than the gap to be repaired. The diameter of the device, if preformed, should be large 25 enough so that it does not exert pressure on the re-growing nerve, but small enough to provide a good seal at the nerve endings. The exact size will depend on the diameter of the nerve to be repaired. Ideally, the device can be formed from a sheet like material of the polymer that can be wrapped around the nerve endings and 30 secured into a nerve conduit channel to make it easier to bring the severed ends together (as opposed to insertion of nerve bundles

into prefabricated tube ends). If desired the polymer may be pre-seeded with cells, such as Schwann cells, and/or combined with a drug or growth factor. Preferably the latter is dispersed evenly throughout the device using a method such as solvent casting, 5 spray drying, or melt extrusion. If necessary, the cells, growth factors or drugs may be encapsulated in the form of microspheres, nanospheres, microparticles and/or microcapsules, and seeded into the porous device.

Non-limiting examples demonstrate methods for preparing 10 the nerve regeneration devices, and the rate of axonal regeneration that can be achieved with these devices.

EXAMPLE 1: Preparation of PHA Porous foam sheet by lyophilization, water extraction.

PHA4400 (Mw 800 K by GPC) was dissolved in dioxane at 15 5% wt/vol. The polymer solution was mixed with sodium particles that had been sieved between 100 and 250 μ m stainless steel sieves. The mixture contained 1 part by weight salt particles and 2 parts polymer solution. A 10-12 g portion of the salt/polymer mixture was poured onto a Mylar® sheet and covered with a 20 second Mylar® sheet separated by a 300-500 steel spacers. The salt/polymer mixture was pressed to a uniform thickness using a Carver press. The mixture was frozen at -26°C between aluminum plates that had been pre-cooled to -26°C. The top Mylar® sheet was removed while keeping the sample frozen. The sample was 25 transferred while frozen to a lyophilizer and was lyophilized overnight to remove the dioxane solvent and yield a PHA4400 foam containing salt particles. The sample was removed from the bottom Mylar® sheet and the salt particles were leached out of the sample into deionized water to yield a sheet of highly porous 30 PHA4400 foam, referred to as Sample A.

EXAMPLE 2: Preparation of PHA Porous foam sheet, lyophilization, surfactant extraction.

A porous foam sheet of PHA4400 was prepared as in example 1, except the salt was leached out into an aqueous 5 solution containing 0.025% Tween 80, rather than water. This was referred to as Sample B.

EXAMPLE 3: Preparation of PHA Porous foam sheet, ethanol extraction of dioxane, water extraction of salt.

PHA4400 (Mw 800 K by GPC) was dissolved in dioxane at 10 5% wt/vol. The polymer solution was mixed with sodium particles that had been sieved between 100 and 250 μ m stainless steel sieves. The mixture contained 1 part salt particles and 2 parts by weight polymer solution. A 10-12 g portion of the salt/polymer mixture was poured onto a Mylar® sheet and covered with a 15 second Mylar® sheet separated by a 300-500 steel spacers. The salt/polymer mixture was pressed to a uniform thickness using a Carver press. The mixture was frozen at -26°C between aluminum plates that had been pre-cooled to -26°C. The top Mylar® sheet was removed while keeping the sample frozen. The sample was 20 transferred while frozen into a bath of cold ethanol (95%) to remove the dioxane solvent and yield a PHA4400 foam containing salt particles. After removal of the dioxane, the sample was removed from the bottom Mylar® sheet and the salt particles were leached out of the sample into deionized water to yield a sheet of 25 highly porous PHA4400 foam, referred to as Sample C..

EXAMPLE 4: Formation of PHA Porous foam sheet, ethanol extraction of dioxane, surfactant extraction of salt.

A porous foam sheet of PHA4400 was prepared as in Example 3, except that the salt was leached out into an aqueous 30 solution containing 0.025% Tween 80, rather than water. This was referred to as Sample D.

EXAMPLE 5: Implantation of Nerve grafts or PHA conduits.

Thirty male Sprague-Dawley rats were divided into 5 groups of 6 animals. A 10 mm segment of the sciatic nerve was exposed in each animal, resected, and then bridged with either an autologous nerve graft or a PHA4400 conduit that was prepared by wrapping the nerve endings with the foams derived from examples 1-4 and thermally melting the edge to form a seal. One group received autologous nerve grafts, each of the remaining groups was implanted with conduits derived from Samples A, B, C or D. Three animals from each group were sacrificed at 10 and 20 days post-operatively, and the repair sites harvested. After fixation the tissue was blocked, sectioned, and then stained with polyclonal antibody to PGP (a pan-neuronal marker) and S100 (an antibody marker for Schwann cells). The axonal and SC (Schwann cell) regeneration distance and area of axonal regeneration were then quantified.

All four samples of PHA4400 handled well, were flexible, had a good tensile strength and held sutures. At the time of harvest there was no evidence of wound infections, no macroscopic evidence of inflammation and no anastomotic failures. At both harvest points the PHA4400 tubes maintained their structure with no evidence of collapse, and the tubes had not adhered to the underlying muscles. Macroscopically there appeared to be no difference between the four PHA4400 samples.

The distance reached into the conduits by the furthest PGP and S100 positive fibers were measured at 10 and 20 days for each group. By 10 days, PGP positive fibers were identified in the distal stump of all four PHA4400 conduits indicating that the 10 mm nerve gaps had been bridged. This indicates an axonal regeneration rate of at least 1 mm/day. A continuous scaffold of

S100 stained fibers across the gaps was also observed. These results were sustained at 20 days.

At 10 days the SC and axons appeared to be regenerating in a straight line through the center of the conduit. At 20 days the 5 quantity of regeneration had increased such that the lumen of the graft, particularly in the proximal half was packed with PGP and S100 positive fibers. The fibers were restricted to the conduit lumen and did not traverse the porous walls of the nerve guides.

At 10 days the greatest percentage area of PGP staining 10 was observed in the PHA4400 – Sample C derived conduits (39.8%) (see Table 1). By 20 days the PHA4400 – Sample D derived conduits supported the greatest percentage of axonal regeneration in the distal stump (55.9%). The greatest progression 15 of regeneration area from 10 to 20 days was obtained in the PHA4400 – Sample B derived conduits with an increase of 86% in the percentage area of axonal regeneration in the distal stump.

20 **Table 1: Percentage of axonal regeneration area in the distal stump at 10 and 20 days for the four different PHA4400 conduits used to repair a 10 mm gap in a rat sciatic nerve.**

CONDUIT DERIVED FROM:	DAYS IMPLANTED	% REGENERATION AREA
PHA4400 – SAMPLE A	10	31.6%
	20	27.2%
PHA4400 – SAMPLE B	10	23.0%
	20	42.8%
PHA4400 – SAMPLE C	10	39.8%
	20	35.8%
PHA4400 – SAMPLE D	10	32.5%
	20	55.9%

From these results it is apparent that the rate of axonal regeneration with conduits derived from PHA4400 is faster and significantly improved over those previously reported for PHB conduits.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet suitable for nerve repair, the pores in the conduit having a diameter of between five and 500 microns, wherein the polymer comprises 4-hydroxybutyrate.
2. The device of claim 1 wherein the polymer is poly-4-hydroxybutyrate.
3. The device of claim 1 wherein the porous conduit comprises a material selected from the group consisting of nerve cells, growth factors, and drugs.
4. A method for preparing a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit tube or sheet suitable for nerve repair wherein the polyhydroxyalkanoate polymer comprises 4-hydroxybutyrate and wherein the device is prepared by thermally induced phase separation of the polymer in a solvent in combination with salt particles, removing the polymer solvent, and removing the salt particles to form pores between five and five hundred microns in diameter.
5. The method of claim 4 comprising leaching with an alcohol followed by leaching with water or a solution comprising a surfactant.
6. The method of claim 4 for preparing the device of claim 1 wherein the device is prepared by a combination of thermally induced phase separation and poragen leaching.
7. The method of claim 5 wherein the surfactant is a polysorbate.
8. A use of a nerve regeneration device for nerve regeneration or repair, wherein the nerve regeneration device comprises a

polyhydroxyalkanoate polymer in the form of a wrapped porous conduit, tube or sheet, the pores in the conduit having a diameter of between five and five hundred microns, wherein the diameter of the conduit is large enough so that it does not exert pressure on a regrowing nerve, but small enough to provide a good seal at the nerve, wherein the polyhydroxyalkanoate comprises 4-hydroxybutyrate.

9. The use of claim 8 wherein the device is prepared in a manner to allow insertion of severed nerve ends into the conduit or wrapping of the nerve ends with the polymer and sealing into the conduit.
10. The use of claim 9 wherein the device sealing is by application of heat.
11. The use of claim 9 wherein the nerves have an axonal regeneration rate of at least 0.8 mm per day across a 10 mm sciatic nerve gap in an animal or human.